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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/846,588	05/01/2001	Steven A. Goldman	19603/3232 (CRF D-2587B)	4784

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/846,588	GOLDMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *10-12,22-24,31,32 and 41-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,13-21,25-30,33-40 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants elected with traverse the invention of Group I (claims 1-9, 13-21, 25-40 and 44-47) in Paper No. 7 dated 4/9/02 is acknowledged.

Applicants argued that the claims of the presently claimed invention are closely related and that they require common areas of search and consideration. Therefore, no serious burden exists for search and examination of all the claims in the Groups set forth in the Office Action dated 2/28/02 in Paper No. 5. Applicants' argument is found unpersuasive because the inventions of Groups I-III differ one from the other because they utilize patentably distinct nucleic acid constructs encoding neurotrophic factors such as the brain-derived neurotrophic factor, neurotrophin-4/5, neurotrophin-3, insulin-like growth factor-1, noggin and an inhibitor of bone morphogenic protein that lack the unity of invention. The encoded neurotrophic factors in Inventions I-III differ in amino acid sequence homology, three-dimensional structures, biochemical properties, and they belong to different families of polypeptide growth factors. The inventions are distinct, each from the other because the encoded neurotrophic factors in Inventions I-III are distinct gene products.

With respect to the issue of further group restriction, Applicants argued that the election requirement is inappropriate because nowhere in Title 35 of the United States Code, Title 37 of the Code of Federal Regulation or The Manual of Patent Examination Procedure sanctions a restriction requirement between different claims dependent from the same independent claim. Applicants' argument is found unpersuasive because MPEP 801.02 indicates that it is proper to require a restriction election where there is

more than one independent and distinct invention in a single application. In this application, a method of treating each neurodegenerative condition selected from the group consisting of Huntington's Disease, Parkinson's Disease, amylotrophic lateral sclerosis, multiple sclerosis, stroke an traumatic injury to the brain and spinal cord appears to constitute a patentably distinct invention. Claims 28-29, 33-45 and 47 link a plurality of patentably distinct groups of neurodegenerative diseases that lack unity of invention. As set forth in MPEP 803.02, unity of invention exists if all species recited in a claim (1) shows a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. Claims 28-29, 33-45 and 47 do not have unity of the invention because a plurality of disclosed patentably distinct groups of neurodegenerative diseases (Huntington's disease, Parkinson's disease, stroke, amyotrophic lateral sclerosis, multiple schlerosis, traumatic injury to the brain and spinal cord) have no common etiology, disease progression, and symptoms. Thus, claims 28-29, 33-45 and 47 are improper written as linking or Markush claims linking multiple distinct inventions. Therefore, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 1-47 are pending in the present application. Claims 10-12, 22-24, 31-32 and 41-43 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 1-9, 13-21, 25-30, 33-40 and 44-47 are examined on the merits herein.

Claim Objections

Claims 6 and 18 are objected to because of the following informalities: the term "promotor" shoud be - - promoter - -. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-30, 33-40 and 44-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, claims 28-30 and 33-40 are drawn to a method of treating Huntington's disease comprising: providing a nucleic acid construct encoding a neurotrophin and injecting the nucleic acid construct into a subject's lateral ventricles or ventricular zone wall under conditions effective to treat Huntington's

disease. Claims 44-47 are directed to a method of treating Huntington's disease comprising providing a neurotrophin and injecting the neurotrophin into a subject's lateral ventricles or ventricular zone wall under conditions effective to Huntington's disease.

The specification teaches by exemplification the construction of a replication defective recombinant adenovirus pAd5-CMV:BDNF:IRES:hGFP expressing brain-derived neurotrophic factor (BDGF) under CMV control and humanized green fluorescent protein (hGFP) under internal ribosomal entry site control. The recombinant adenovirus was injected into the lateral ventricles of adult rats that were treated for 18 days thereafter with the mitotic marker bromodeoxyuridine (BrdU). Three weeks after injection, ELISA analysis revealed that the cerebral synovial fluid BDNF level of AdBDNF-injected animals was about 1 ug/g, whereas BDNF was undetectable in cerebral synovial fluid (CSF) of control animals. *In situ* hybridization revealed that BDNF and GFP mRNAs were largely restricted to the ventricular wall (ependymal surface). In AdBDNF-injected rats, the olfactory bulb exhibited a 2.44-fold increase in the number of BrdU+-βIII tubulin+ neurons relative to AdNull (AdCMV:hGFP) controls. Additionally, ventricular AdBDNF infection also induced neuronal recruitment to the neostriatum as evidenced by the presence of BrdU+-βIII tubulin+ neurons, many of which also expressed glutamic acid decarboxylase, cabindin-D28 and DARPP-32, markers of medium spiny neurons of the neostriatum. These newly generated neurons survived at least 5-8 weeks after viral induction.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention which is drawn to a method of treating Huntington's disease by injecting a nucleic acid construct encoding a neurotrophin or a neurotrophin into a subject's lateral ventricles or ventricular zone wall under conditions effective to treat said disease for the reasons to be discussed below.

At the effective filing date of the present application (05/01/2000), the art for treating any neurodegenerative disease using *in vivo* gene therapy or any neurotrophic factor remains immature and unpredictable with respect to the attainment of therapeutic effects, let alone for treating specifically Huntington's disease. This is evidenced by the reviews of During et al. (Mol. Med. Today 4:485-493, 1998) and Shihabuddin et al. (Mol. Med. Today 5:474-480, 1999). During et al. stated "Which neurological disease are the best targets for gene therapy, given that currently targeted neurological diseases are determined largely by the availability of animal models and might not be the most responsive to a gene therapy approach?" and "How well do current animal models of central nervous system (CNS) disease predict clinical efficacy of novel therapeutic strategies?" (page 490, in "The outstanding questions"). With respect to claims drawn to *in vivo* gene therapy, it is also well known in the art that the lack of optimal vectors, the lack of stable *in vivo* transgene expression as well as the adverse host immune responses against delivered vectors are some of factors limiting the effectiveness of gene therapy to achieving therapeutic effects. As the term "treatment" encompasses delaying, slowing, abrogating and reverse the progression of the Huntington's disease, the instant specification fails to offer any guidance for a skilled artisan on how to

achieve any of the aforementioned therapeutic effects. There is no correlation between the reported presence of BrdU+-βIII tubulin+ neurons in the neostriatum with any of the therapeutic effects contemplated by Applicants. This is because there is no evidence of record indicating or suggesting that an efficient number of striated neurons in the appropriate location of the brain has been generated to yield any therapeutic effects. Additionally, it is unclear whether these newly induced striated neurons can form functional junctions with preexisting neurons or that these newly generated striated neurons can survive better than the neurons they intend to replace for any significant period of time under the disease conditions to yield any desired therapeutic effects. The present disclosure also fails to provide any *in vivo* example (part of guidance) showing any therapeutic effects for Huntington's disease has been achieved or attained for the instantly claimed invention. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so. With the lack of guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

The instant claims encompass the use of any neurotrophins for attaining therapeutic effects for Huntington's disease. The instant specification is not enabled for such a claimed invention. Again, neither the instant specification nor the prior art at the effective filing date of the present application teach that other members of the neurotrophin family such as neurotrophin-3, neurotrophin-4, neurotrophin-6, nerve growth factor (NGF) are also capable of effecting neurogenesis in post-natal and adult

brain to the same extent as shown for brain derived neurotrophic factor (BDNF), let alone for attaining any therapeutic effects. Kirschenbaum et al. (Proc. Natl. Acad. Sci. USA 92:210-214, 1995) teach that BDNF is the only neurotrophin tested (BDNF, neurotrophin-3, NGF) that can affect the differentiation and survival of newly generated neurons in the adult rat brain *in vitro* (see abstract and Table 1). The enhanced neuronal survival property of BDNF is also controversial since Ahmed et al. (J. Neurosci. 15:5765-5778, 1995) have demonstrated that BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronal precursors (see abstract). It should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

As such, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

With respect to claims 44-47, in addition to the issues discussed above, it is noted that the instant specification offers no guidance for a skilled artisan on the effective amount of any neurotrophins to be injected into a subject's lateral ventricles or ventricular zone wall, or the frequency of injections to obtain any therapeutic effects for Huntington's disease. There is no teaching regarding on how an effective amount of

any neurotrophin can be maintained in the affected brain region, particularly the globus pallidus, the substantia nigra, substantia innominate, ventral pallidum, caudate and putamen and others, for a sufficient period of time to elicit the desired therapeutic effects. As such, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Accordingly, due to the lack of direction or guidance provided by the specification regarding to the issues set forth above, the unpredictability of the gene therapy art and physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

Claims 1-9, 13-21 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing neuronal production or recruiting neurons to a subject's olfactory bulb and neostiatum in post-natal and adult brain comprising: providing a nucleic acid construct encoding a brain derived neurotrophic factor (BDNF) and injecting the nucleic acid construct into a subject's lateral ventricles or ventricular zone wall under conditions effective to express the BDNF and to induce neuronal production or to recruit neurons to said subject's olfactory bulb and neostriatum, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

With respect to the elected invention, claims 1-9 are directed to a method of inducing neuronal production in post-natal and adult brain and spinal cord comprising: providing a nucleic acid construct encoding a neurotrophin and injecting the nucleic acid construct into a subject's lateral ventricles or ventricular zone wall under conditions effective to express the neurotrophin and to induce neuronal production in the brain and spinal cord of the subject. Claims 13-21 and 25-27 are directed to a method of recruiting neurons to a subject's brain comprising: providing a nucleic acid construct encoding a neurotrophin and injecting the nucleic acid construct into the subject's lateral ventricles or ventricular zone wall under conditions effective to express the neurotrophin and to recruit neurons to the brain of the subject.

With respect to claims 1-9 encompassing neuronal production in both post-natal and adult brain and spinal cord using any neurotrophins, the instant specification is not enabled for such a broadly claimed invention. This is because there is no evidence of record indicating or suggesting that any neuronal production has been induced in the spinal cord. Additionally, as already noted above neither the instant specification nor the prior art at the effective filing date of the present application teach that other members of the neurotrophin family such as neurotrophin-3, neurotrophin-4, neurotrophin-6, nerve growth factor (NGF) are also capable of effecting neurogenesis in post-natal and adult brain to the same extent as shown for brain derived neurotrophic factor (BDNF). Kirschenbaum et al. (Proc. Natl. Acad. Sci. USA 92:210-214, 1995)

teach that BDNF is the only neurotrophin tested (BDNF, neurotrophin-3, NGF) that can affect the differentiation and survival of newly generated neurons in the adult rat brain *in vitro* (see abstract and Table 1). The enhanced neuronal survival property of BDNF is also controversial since Ahmed et al. (J. Neurosci. 15:5765-5778, 1995) have demonstrated that BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronal precursors (see abstract). It should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

As such, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

The instant claims also encompass a method of inducing neuronal production in any region of a post-natal and adult brain and spinal cord, and to recruit neurons to any specific region of a subject's brain (e.g., the basal ganglia of the brain, the caudate nucleus, the putamen, the globus pallidus, the cortex) using any neurotrophins, the instant specification is not enabled for such a broadly claimed invention. Apart from the exemplification showing an increased neuronal production and recruitment to the olfactory bulb and to a lesser extent to the neostriatum by injecting a replication

defective recombinant adenovirus expressing BDNF into the lateral ventricles of adult rats, there is no evidence indicating that any significant numbers of induced neurons of any beneficial uses have been generated (in comparison with proper control animals) in any region of the brain and spinal cord, particularly to specific regions of the brain contemplated by Applicants, by BDNF, let alone by any other neurotrophins. Applicants are invited to point out the specific page numbers and line numbers where the neuronal recruitment to specific contemplated brain regions has been attained, or neuronal production in any region of the brain and spinal cord has been achieved. Since the prior art at the effective filing date of the present application does not provide such guidance, and in light of the complexity of the brain physiology, it is incumbent upon the instant specification to do so. Again, with the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the full scope of the method as claimed.

Accordingly, due to the lack of direction or guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 contains an improper Markush language in the phrase "basal ganglia of the brain, the caudate nucleus, the putamen, and/or the globus pallidus". It is unclear which combinations of the recited locations that the claim refers to. Therefore, the metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 7, 13-17, 19 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss et al. (U.S. Patent No. 6,071,889 with an effective filing date of 6/7/1995).

Weiss et al. teach a method for administering a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral

ventricle of the forebrain, of a mammal (juvenile and adult) to induce the proliferation and differentiation of neural cells *in vivo* (see Summary of Invention, cols. 26-29; and the claims). Weiss et al. also disclose that any expression vector known in the art can be used to express BDNF as long as it has a promoter that is active in the cell, and appropriate termination and polyadenylation signals. Expression vectors such as retroviral vectors, adenovirus vectors, adeno-associated virus vectors, HSV vectors, vaccinia virus vectors and others (col. 29, lines 44-57; col. 20, lines 61-63); mammalian cell specific promoters such as those of tyrosine hydroxylase, DBH, GFAP, NSE, NF, phenylethanolamine N-methyltransferase as well as retroviral LTR, SV40 and CMV promoters can be utilized (col. 29, lines 17-25). Since Weiss et al. teach a method having the same steps and the same starting materials, it is inherently that neuronal production in post-natal and adult brain as well as the recruitment of neurons to the olfactory bulb would also be obtained.

Accordingly, Weiss et al. anticipate the instant claims.

Claims 1-4, 7, 13-16, 19 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Benraiss et al. (Society for Neuroscience 25, 413.3, 1999).

Benraiss et al. teach a single lateral ventricular injection of a BDNF-expressing adenovirus under the control of a CMV promoter substantially augmented the recruitment of new neurons into the olfactory bulbs of an adult rat brain in comparison with the controlled animals (see the abstract).

Therefore, Benraiss et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7, 13-16, 19 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zigova et al. (Molecular and Cellular Neuroscience 11:234-245, 1998) in view of Bajocchi et al. (Nature Genetics 3:229-234, 1993) and Yancopoulos et al. (U.S. Patent No. 5,453,361).

Within the enabled scope of the presently claimed invention, Zigova et al. teach that intraventricular administration of BDNF for 12 days into the right lateral ventricle of adult rat brains resulted in increased numbers of newly generated neurons in the adult

Olfactory bulb (see abstract and the entire article). Zigova et al. do not teach the use of a nucleic acid construct encoding BDNF in their study.

At the effective filing date of the present application, Bajocchi et al. already teach an *in vivo* gene transfer via lateral ventricle administration to ependymal cells in the central nervous system of a rat using a recombinant adenovirus vector. Bajocchi et al. also do not teach the use of a nucleic acid molecule encoding BDNF for *in vivo* delivery to ependymal cells to induce neuronal production or to recruit neurons to the olfactory bulb in post-natal and adult brain. However, Bajocchi et al. teach that the ependymal cells lining the ventricles are a particular useful target for CNS directed gene transfer where the goal is to deliver proteins/peptides to the brain, and that the anatomic location of the ependymal layer permits secretion of proteins/peptides to the CSF and thus indirectly to the brain. Bajocchi et al. further teach that one advantage of *in vivo* gene transfer to the ependymal layer over direct administration to the gene product to the CNS is that the gene transfer provides a local site of production of the gene product because macromolecules administered to the CNS turn over rapidly (see page 232, col. 1, top of first full paragraph). Yancopoulos et al. already disclose nucleic acid sequences and vectors expressing BDNF (see the entire patent).

Accordingly, at filing date of the present application it would have been obvious and within the scope of skills for an ordinary skilled artisan to modify the method taught by Zigova et al. by injecting a recombinant adenovirus vector expressing BDNF into the right lateral ventricle of adult rat brains to induce neurogenesis in the adult olfactory bulb instead of infusion of BDNF in light of the teachings of Bajocchi et al. and Yancopoulos

et al. An ordinary skilled artisan would have been motivated to make this modification because Bajocchi et al. teach that an advantage of *in vivo* gene transfer via intraventricular administration to the ependymal layer over direct administration of a gene product to the CNS, for this instance BDNF, is that the gene transfer provides a local site of production of the gene product whereas the gene product administered to the CNS turns over rapidly. Moreover, one of ordinary skilled artisan would also have been motivated to carry out the above modification to investigate the application of BDNF gene delivery to neuronal replacement in a diseased animal model. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 6, 13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Weiss et al. (U.S. Patent No. 6,071,889 with an effective filing date of 6/7/1995) in view of Rosenthal (U.S. Patent No. 5,830,858) and Zigova et al. (Molecular and Cellular Neuroscience 11:234-245, 1998).

Within the enabled scope of the presently claimed invention, Weiss et al. teach a method for administering a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral ventricle of the forebrain, of a mammal (juvenile and adult) to induce the proliferation and differentiation of neural cells *in vivo* (see Summary of Invention, cols. 26-29; and the claims). Weiss et al. also disclose that any expression vector known in the art can be used to express BDNF as long as it has a promoter that is active in the cell, and appropriate termination and

polyadenylation signals. Expression vectors such as retroviral vectors, adenovirus vectors, adeno-associated virus vectors, HSV vectors, vaccinia virus vectors and others (col. 29, lines 44-57; col. 20, lines 61-63); mammalian cell specific promoters such as those of tyrosine hydroxylase, DBH, GFAP, NSE, NF, phenylethanolamine N-methyltransferase as well as retroviral LTR, SV40 and CMV promoters can be utilized (col. 29, lines 17-25). However, Weiss et al. do not specifically teach the use of any inducible or conditional promoter for expressing BDNF or that their method would result in inducing neuronal production or neuronal recruitment to the olfactory bulb of a subject's brain.

However, at the effective filing date of the present application Rosenthal teaches the use of inducible eukaryotic promoters for expressing neurotrophic factors, including NT-4 and BDNF (col. 12, lines 14-33; col. 13, lines 7-28). Additionally, Zigova et al. also teach that intraventricular administration of BDNF for 12 days into the right lateral ventricle of adult rat brains resulted in increased numbers of newly generated neurons in the adult Olfactory bulb.

Accordingly, at filing date of the present application it would have been obvious and within the scope of skills for an ordinary skilled artisan to modify the method taught by Weiss et al. by utilizing an inducible promoter for expressing BDNF based on the teachings of Rosenthal. An ordinary skilled artisan would have been motivated to make this modification simply because of a designer's choice. One of ordinary skilled artisan would have a reasonable expectation of success that the modified method would result in inducing neuronal production or neuronal recruitment to the olfactory bulb of a

subject's brain because Zigova et al. also demonstrated that intraventricular administration of BDNF for 12 days into the right lateral ventricle of adult rat brains resulted in increased numbers of newly generated neurons in the adult Olfactory bulb.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
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